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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/455,540	12/07/99	BESSETTE	45112-045

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EXAMINER	
PATTEN,P	
ART UNIT	**PAPER NUMBER**
1651	9

DATE MAILED: 01/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/455,453	Applicant(s) Bessette et al.
	Examiner Patricia Patten	Group Art Unit 1651

Responsive to communication(s) filed on _____ .

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) 1-15 is/are pending in the application.

Of the above, claim(s) 15 is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) 1-14 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____ .

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

X Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

Applicants had indicated in the Response to the restriction requirement in Paper No. 8 that they elected the species cAMP/PKA activator, however, cAMP/PKA activators were not in the Claims as originally filed, nor were amongst the species presented for election in Paper No. 6. A telephone call was made to Attorney Willem Gadiano on 01/24/2001, whereby he elected the species cAMP/cAMP-dependent protein kinase for examination on the merits.

Applicant's election with traverse of Group I, Claims 1-14 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that it would not be a serious burden on the examiner to search both inventions concurrently because the method for using (Group II)is drawn specifically to the composition of Group I. This is not found persuasive because, as pointed out in the Restriction requirement sent 7/06/2000, the method may be carried out with numerous other pharmaceuticals known in the art such as cytokines. Thus, the search for each of the above inventions is not co-extensive particularly with regard to the literature search. Further, a reference which would anticipate the invention of one group would not necessarily anticipate or even make obvious another group.

Because these inventions are distinct for the reasons given above and the search required for each Group is not required for the others, restriction for examination purposes as indicated is proper.

Applicant is advised that the response to this requirement, to be complete, must include an election of the invention to be examined even though the requirement be traversed.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-15 are pending in the application.

Claim 15 has been withdrawn as being directed towards a non-elected invention.

Claims 1-14 have been presented for examination on the merits.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-15 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-3 and 5-16 of copending Application No. 09/455,544. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the term 'transduction modulator.' It is unclear exactly what 'transduction modulators' are because they are not well defined in the specification. The Specification teaches that 'transduction modulators' can be selected from plant phytochemicals such as forskolin, or from proteins such as PKC. It is known that forskolin is a cAMP activator, however, it is not thought that forskolin is known as 'transduction modulators.' The term 'transduction modulator' is further indefinite in that if 'transduction modulators' are any compound which would have an

effect on the cAMP signal transduction pathway, then there would be a countless number of compounds which would in fact perform this function. However, the mechanisms of each and every 'transduction modulator' is not known, and therefore, the term 'transduction modulator' is not clearly delineated in the claim. Clarification is necessary.

Claim 3 recites 'cAMP/cAMP-dependent protein kinase.' The Examiner belives that this is a complex, but is not sure. Clarification is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a plant essential oil compound which is known in the art for treating cancer or abnormal cell proliferation, such as monoterpines (eugenol), along with growth factor receptor inhibitors such as FGF inhibitor, does not reasonably provide enablement for any plant oil compound or any plant oil compound specifically recited in the Markush Group of plant essential oil compounds in Claim 2, in combination with a signal transduction modulator such as cAMP/cAMP-dependent protein kinase, tyrosine kinase, calcium

phospholipid-dependent protein kinase, mitogen activated protein kinase family members or calcium-calmodulin-dependent protein kinase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Inventions targeted for human therapy bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. The standard of enablement is higher for such inventions because effective treatments for disease conditions are relatively rare, and may be unbelievable in the absence of strong supporting evidence. Claims drawn to pharmaceutically acceptable compositions and to methods of administering compounds to humans generally require supporting evidence because of the unpredictability in biological responses to therapeutic treatments.

Plant essential oil compounds such as monoterpenes are known in the art to exhibit cell growth inhibition. However, it would be highly unpredictable to ascertain whether **any** plant essential oil compound (Claim 1), or any plant essential oil compound found in the Markush Group of Claim 2 would effectively inhibit abnormal cell proliferation. The state of the art regarding cancer treatments is unpredictable. As of yet, there is no cure for cancer despite rigourous pharmaceutical research and experimentation. Bally et al. (US 5,595,756) stated that " Despite enormous investments of financial and human resources, no cure exists for a variety of diseases. For example, cancer remains one of the major causes of death. A number of bioactive agents have been found, to varying degrees, to be effective against tumor cells. However, the clinical use of such antitumor agents has been highly compromised because of treatment-limiting toxicities" (Col.1 lines 17-24).

Thus, In order to acertain the effectiveness of a compound in the treatment for abnormal cell proliferation, one would need to provide substantial evidence of such. The Instant

specification lacks critical guidance with respect to any plant essential oil compounds, besides the ones clearly displayed in the Specification (thymol, isoeugenol, eugenol and cinnamic aldehyde) and those already known in the art (monoterpenes) which would function commenserate in scope with the claimed invention. Benzyl alcohol for example, which is found in the Markush group in Claim 3, is a well known alcohol which is purified from plant essential oils. Benzyl alcohol is not a monoterpene. Although benzyl alcohol is known to be used in the art as a carrier for pharmaceutical compositions , teachings where benzyl alcohol inhibits cell proliferation could not be found in the art. Furthermore, as evidenced by the data provided in the Instant specification itself, plant essential oils are unpredictable with regard to inhibition of cell proliferation (Figure 3).

Absent such critical guidance with respect to **any** plant oil essential compounds, or any of the plant essential oil compounds in Claim 3 besides those shown in the specification and/or known in the prior art for effectively inhibiting cell proliferation, one of skill in the art would necessarily be required to put forth a substantial inventive contribution in order to acertain whether or not all of the compounds in the Markush group of Claim 3, as well as any other plant essential oil compounds, would function as effectively as those plant essential oils already known, or displayed in the Instant specification to have a beneficial effect with regard to cancer or tumor inhibition.

The Instant claims are enabled for certain growth factor receptor inhibitors in the composition because it is known in the art that certain growth factor inhibitors such as FGF inhibitors decrease cell proliferation (Please see Bernfield et al. US 6,028,061). However, signal

transduction modulators such as calcium phospholipid-dependent protein kinase, cAMP/cAMP-dependent protein kinase and mitogen activated protein kinase family members are not found in the art for inhibiting abnormal cell proliferation as with cancers and thus are deemed non-enabled as discussed *vide infra*.

Typically, research as shown that **inhibitors** of protein kinases such as certain cAMP analogs as described by Clardiello et al. (1999) have a beneficial effect on abnormal cell proliferation (Please see pp. 821, where they discuss that PKAI is inhibited by the site selective cAMP analog 8-chloro-cAMP, which in turn induced growth inhibition *in vitro* and *in vivo*). Thus, the claims as instantly presented, appear to contradict the prior art. Compositions containing protein kinases and/or cAMP/cAMP dependent protein kinase complexes for decreasing cell proliferation were not found in the prior art. Because cell proliferation is a highly complex, unpredictable regulated system, claims to a composition comprising a material such as a protein kinase which seems to contradict the prior art teachings, would necessarily need to provide clear, sufficient evidence within the Disclosure in order to substantiate such claims. The Disclosure as Instantly filed fails to provide such evidence. Lacking this evidence, one of skill in the art would need to perform undue experimentation entailing rigourous trial and error protocols in order to acertain if, and how protein kinases would work commensurate in scope with the claimed invention.

It has been well established that :disclosure in an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves." In re Gardner et al., 166 USPQ 138 (CCPA 1970).

All of these factors were addressed in the initial rejection. Breadth alone is not the issue, however. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Marty (GB 2,151,924 A). Claim 1 is drawn to a composition for treating soft tissue cancer comprising a plant essential oil compound and a signal transduction modulator.

Marty (GB 2,151,924 A) disclosed a composition which contained primrose oil along with cyclic AMP (a signal transduction modulator) (Please see Claims 1-9).

Primrose oil would have inherently contained 'plant essential oil compounds.'

The language 'for the prevention or treatment of soft tissue cancer' is merely an intended use for a known composition which does not materially change the composition.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernfield et al. (US 6,028,061) taken with Yakota et al. (1986) and further in view of (Bardon et al. 1998). Claims 1-8 and 10-14 are drawn to a composition comprising a plant essential oil compound and a signal transduction modulator such as growth factor receptor inhibitors. Claims are further drawn to specific plant essential oil compounds such as isoeuegenol and carvacrol for example.

Bernfield et al. (US 6,028,061) taught that inhibition of the angiogenesis promoting agent - fibroblast growth factor (FGF) with inhibitors such as glycosaminoglycan decreased angiogenesis (cell proliferation) which consequently could have been used in tumor growth inhibition (Col.2, lines 58-65 and Col.3, lines 1-6).

Yokota et al. (1986) disclosed that eugenol was useful in inhibiting cell proliferation when administered to mutagenically exposed rats (See Table 2).

Bardon et al.(1998) taught that monoterpenes inhibited the growth of breast cancer cell proliferation (See Figures 1-4).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is l

known in the art to inhibit abnormal cell proliferation. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, *In re Sussman*, 1943 C.D. 518.

Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above cited references before him.

Because all of the compounds in claims 6-8 and 10-14 are monoterpenes, one of ordinary skill in the art would have had a reasonable expectation that they would have functioned similarly to the monoterpenes disclosed by Bardon et al. Because monoterpenes were known in the art for inhibiting abnormal cell proliferation, one would have been motivated to have added monoterpenes such as thymol or carvacrol into a pharmaceutical preparation in order to beneficially treat abnormal cell proliferation.

The language 'for the prevention or treatment of soft tissue cancer' or 'wherein the soft tissue cancer is breast cancer' (as in Claim 5) are merely intended uses for the composition which does not materially change the composition.

Addition of carriers to pharmaceutical preparations was routine in the art at the time of the Instant invention. One of ordinary skill in the art would have been motivated to have added a carrier to the composition for mere ease of administration.

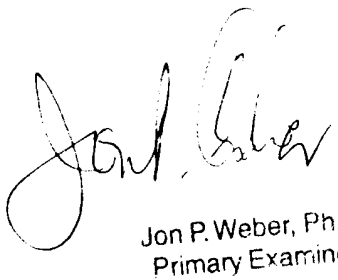
From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Patricia Patten, whose telephone number is (703)308-1189. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Jon P. Weber, Ph.D
Primary Examiner